Aplastic Anemia: Current Thinking on the Disease, Diagnosis, and Non-Transplant Treatment

AA & MDS International Foundation
2014 Living with Aplastic Anemia, MDS, or PNH Patient and Family Conferences
(Los Angeles California)
April 5, 2014

Objectives

• To give a brief historical overview of AA
• To provide a general overview of the diagnosis and pathogenesis of aplastic anemia (AA)
• To discuss the treatment approach for newly diagnosed AA patients
• To discuss the treatment approach for relapsed/refractory AA patients
• To discuss the common side effects encountered with specific pharmacologic therapies used in AA

Historical Perspective

Timeline

1888
Paul Ehrlich described the 1st case of Aplastic Anemia
A young woman who died suddenly after an abrupt illness characterized by anemia, bleeding, fever, and hypocellular BM

1899
Anti-lymphocyte activity of Anti-Lymphocyte Serum (ALS) first described by Metchnikoff

1904
Chauffard was the first to use the term Aplastic Anemia

1972
1st Allogeneic Bone Marrow Transplant Performed It was performed on a patient with Aplastic Anemia

Overview

Natural History of Aplastic Anemia

32% at time of dx of AA

PNH

Aplastic Anemia

MDS/AML

Disease Severity

sAA and vAA

Moderate AA

Time from Diagnosis of AA (Years)

Maciejewski JP et al. JBU. 2011
Maciejewski JP et al. Leuk & Lymph. 2004
Decision to treat: Based on Disease Severity

Epidemiology of AA
- 2-4 per 1 million individuals per year (US)
- 2-3 fold higher in Asia

Diagnosis of AA
- Hypocellular bone marrow (<30%)
- Cytopenias
- Normal karyotype by metaphase cytogenetics (in general)

1) <30% BM cellularity
And at least 2 of the ff:
1) ANC <0.5 x 10^9/L
2) Platelet count <20 x 10^9/L
3) Retic count <60 x 10^9/L

1) <30% BM cellularity
And depressed counts but did not
reach criteria for severe AA

Subset
Chronic moderate AA: >3 months
Severe AA
Very Severe AA

Epidemiology of AA
- 2-4 per 1 million individuals per year
- 2-3 fold higher in Asia

Causes of Aplastic Anemia
1) Idiopathic Aplastic anemia
2) Secondary Aplastic Anemia
   - Radiation
   - Viruses
   - Hepatitis Virus
   - Immune Deficiency
   - Thrombosis
   - Eosinophilic fascitis
   - Hypogammaglobulinemia
   - Pregnancy
   - Drugs and Chemicals
     - Idiosyncratic Reaction
     - Chloramphenicol
     - NSAIDs
     - Gold
     - Anti-epileptic medications
     - Regular Effects
     - Cytotoxic agents
     - Benzene

Pathogenesis
- Immune cause of AA was inferred based on:
  - Response to immunosuppressive therapy
  - Demonstration of immune activation
  - Animal models

Immune Pathogenesis
- Anergy Inducers
  - CTLA-4-Ig
  - Anti-CD154
- Cytostatics
  - MMF
  - AZA
  - PUVA/ ECP
- Depleting Agents
  - ATG/ALG
  - Alemtuzumab
  - Visilizumab
- Anti-cytokines
  - Etanercept
  - Infliximab
  - Fontolizumab
Overview

How to treat AA?

Severe AA or Very Severe AA

Age ≥ 40 years old
With Matched Sibling Donor

Age < 40 years old
No Matched Sibling Donor

Bone Marrow Transplant
Immunosuppression

Non-Transplant Pharmacologic Options

Non-Transplant Pharmacologic Treatments (sAA)

Anti-Thymocyte Globulin/ Anti-Lymphocyte Globulin

- Polyclonal purified IgG fraction of sera from animals like rabbit, horse or rarely goats that are immunized with human thymocytes or T cell lines
- Mainstay in the treatment of severe AA or very severe AA
- Combined with cyclosporine or tacrolimus for the treatment of AA
- Results in 70-80% overall response rate in the frontline setting
- Can be used in the salvage setting
- Available as rabbit or horse

Mechanism of Action

Stem cells

Virus

Unknown Antigens

TCR

CD28

T cells

Virus

Thymus

T cell Lines

Effector Mechanisms

Expanded Effector T cells

APC

Calcineurin Inhibitors

- Cyclosporine
- Tacrolimus

ATG + Cyclosporine

Treatment Options

Calcineurin Inhibitors
- Cyclosporine
- Tacrolimus

Depressing Agents
- ATG/ALG

Stem cells

Native T cells

Activated T cells

Effector T cells

Expanded Effector T cells
Non-Transplant Pharmacologic Treatments (sAA)

How can we improve these results?

Strategies Employed
1) Use a different ATG
2) Add Additional Agents
3) Use a completely different Agent/Pathway

4 Goals in sAA Treatment
11 year follow-up

Try a Different ATG

Rabbit Anti-Thymocyte Globulin (rATG) – Relapsed/Refractory setting

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of AA</th>
<th>Median Age (y)</th>
<th>Other Treatment</th>
<th>Dose</th>
<th>Response Rate</th>
<th>Survival % (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schonberg et al., BJH. 2006, N=43</td>
<td>Relapsed/refractory</td>
<td>42 (32-72)</td>
<td>Sericinum (500 µg/kg) or rATG (150 µg/kg daily)</td>
<td>0.5 mg/kg D1 x 5 D</td>
<td>85%</td>
<td>60% (8-75)</td>
</tr>
<tr>
<td>D. Brice, E. et al., EHA 2015, N=30</td>
<td>Refractory follow-up with rATG</td>
<td>21 (12-67)</td>
<td>CsA 5 mg/kg PO D1-180</td>
<td>3.5 mg/kg D1 x 5 D</td>
<td>70%</td>
<td>93% (~30 mos)</td>
</tr>
</tbody>
</table>

Which ATG is better? Horse ATG or Rabbit ATG?
## Non-Transplant Pharmacologic Treatments (sAA)

### Horse ATG vs Rabbit Anti-Thymocyte Globulin

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Median Age (y)</th>
<th>Treatment Schema</th>
<th>Dose</th>
<th>Response Rate</th>
<th>Survival % (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atta EH et al. 2010. Ann Hematol</td>
<td>Retrospective</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>ORR at 6 mos = 50% (hATG) vs 35% (rATG)</td>
<td>p=0.05</td>
</tr>
<tr>
<td>Zheng Y et al. 2006. Exp Hematol</td>
<td>Randomized</td>
<td>34 (2-71)</td>
<td>Arm 1=hATG, Arm 2=hATG + CsA, Arm 3=hATG+rhuGM-CSF/rhu-EPO, Arm 4=rATG+rhuGM-CSF/rhu-EPO</td>
<td>Arm 1=12 mg/kg/day x 5 D, Arm 2=CsA 5 mg/kg/D x 6 mos and maintenance 2.5 mg/kg/D x 6 mos, Arm 3 †, Arm 4 5 mg/kg/D IV D1-5</td>
<td>ORR Arm1=58%, Arm2=79%, Arm3=73%, Arm4=53%</td>
<td>5 yr act surv Arm1=58%, Arm2=81%, Arm3=80%, Arm4=66%</td>
</tr>
</tbody>
</table>

† rhuGM-CSF- 5μg/kd/D SC started on Day31 was administered 3 days a week for the first month, 2 days/week for the 2nd month, 1 day/week during the 3rd month

rhuEPO 100 units/kg/D IV x 3 days/week x 1st month, 2 days/week x 2nd month, 1 day/week x 3rd month

**A. Comparison of Treatment Responses between 4 treatment arms**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Cis</th>
<th>EST Regimen</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>NR (%)</th>
<th>The overall response rate (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>hATG</td>
<td>&gt;EATG</td>
<td>14</td>
<td>14</td>
<td>76.0</td>
<td>57.0</td>
<td>0.01 (1 vs 2)</td>
</tr>
<tr>
<td>Group 2</td>
<td>EATG+CsA</td>
<td>&gt;EATG+CsA</td>
<td>76.0</td>
<td>49.4</td>
<td>&lt;0.001 (1 vs 2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>EATG+CSF-rhuGM-CSF/rhu-EPO</td>
<td>&gt;EATG+CSF-rhuGM-CSF/rhu-EPO</td>
<td>76.0</td>
<td>49.4</td>
<td>&lt;0.001 (1 vs 2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 4</td>
<td>rATG+CSF-rhuGM-CSF/rhu-EPO</td>
<td>&gt;rATG+CSF-rhuGM-CSF/rhu-EPO</td>
<td>76.0</td>
<td>49.4</td>
<td>&lt;0.001 (1 vs 2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**B. Overall Survival by Kaplan Meier Estimate of 4 treatment arms**

12 months actuarial survival

<table>
<thead>
<tr>
<th>TxArm</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1=70%</td>
<td>0.01 (1 vs 2)</td>
</tr>
<tr>
<td>Arm 2=91%</td>
<td>0.2 (1 vs 2)</td>
</tr>
<tr>
<td>Arm 3=83%</td>
<td>0.4 (1 vs 4)</td>
</tr>
</tbody>
</table>

60 months actuarial survival

<table>
<thead>
<tr>
<th>TxArm</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1=58%</td>
<td>&lt;0.001 (1 vs 2)</td>
</tr>
<tr>
<td>Arm 2=81%</td>
<td>0.003 (1 vs 3)</td>
</tr>
<tr>
<td>Arm 4=66%</td>
<td>0.505 (1 vs 4)</td>
</tr>
</tbody>
</table>

Afable M et al. Haematologica. 2011

Scheinberg et al. NEJM. 2011
Non-Transplant Pharmacologic Treatments (sAA)

Horse ATG vs Rabbit Anti-Thymocyte Globulin

A. Comparison of Treatment Responses at 3 mos and 6 mos

<table>
<thead>
<tr>
<th>Response</th>
<th>Horse ATG (N=60)</th>
<th>95% CI</th>
<th>Rabbit ATG (N=50)</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ns (%)</td>
<td></td>
<td>ns (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 3 mo</td>
<td>37 (62)</td>
<td>49–74</td>
<td>20 (33)</td>
<td>21–46</td>
<td>0.002</td>
</tr>
<tr>
<td>At 6 mo</td>
<td>41 (68)</td>
<td>56–80</td>
<td>22 (37)</td>
<td>24–49</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Side Effects associated with ATG Therapy

- Decrease in Blood Counts (Blood Transfusions, bleeding and infections)
- Serum Sickness
- Abnormalities in liver enzymes
- Abnormalities in kidney function

Common Side Effects associated with Cyclosporine therapy

- High Blood Pressure
- Kidney Problems (Renal insufficiency)
- Thickening of the gums (gingival hyperplasia)
- Peripheral neuropathy
- Infections
- Headaches
- Tremors

Add New Agents
Add New Agents

Mycophenolate Mofetil

- Blocks proliferation of activated T cells by inhibition of inosine monophosphate Dehydrogenase (IMPDH)
- Has been used as a kidney sparing immunosuppressant as an adjunct to CsA in renal and other solid organ transplantation
- May induce tolerance to allografts
- Dose tested in phase II single arm trial in the NIH is 600 mg/m² PO once daily starting on Day 1 for 18 months. This was given in conjunction with hATG + CsA.

Scheinberg P. et al. BJH. 2005

Sirolimus

- Inhibits the mammalian target of rapamycin (m-TOR) pathway
- May work through a non-calcium dependent calcineurin inhibitor
- Dose tested in phase III randomized trial in the NIH is 2 mg PO once daily starting on Day 1 for 6 months.
- Associated with hypertriglyceridemia and hypercholesterolemia

Non-Transplant Pharmacologic Treatments (sAA)

Try New Non-ATG based Treatments

Alemtuzumab
- Selectively kills CD-52 bearing cells via ADCC and complement mediated lysis
- CD-52 is a GPI linked molecule expressed in T, B, and Dendritic cells but not on Langerhan cells and not on dermal interstitial DC
- Drug can be given subcutaneously
- CMV reactivation is a concern during therapy

Alemtuzumab (Campath) - Frontline setting

<table>
<thead>
<tr>
<th>Study Descr</th>
<th>Median Age (y)</th>
<th>Additional Treatment</th>
<th>Dose</th>
<th>Response Rate (%)</th>
<th>Survival % (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risitano A et al. Milano SIE Meeting. 2009</td>
<td>65</td>
<td>Cyclosporine 2 mg/kg BID x 3 mos</td>
<td>50 mg bi-day</td>
<td>3-10-30-30-(30) x 4-5 days for SAA</td>
<td>ORR 4/6 (66%) CR 3/6 (50%) PR 1/6 (17%) 80% (40 mos)</td>
</tr>
<tr>
<td>Gomez-Almaguer D et al. Ann Hematol. 2010</td>
<td>50</td>
<td>Cyclosporine 2 mg/kg BID x 5 days</td>
<td>10 mg SC daily</td>
<td>ORR 8/14 (57%) CR 2/14 (14%) PR 6/14 (43%) 71% (38 mos)</td>
<td></td>
</tr>
<tr>
<td>Kim H et al. Leuk Res. 2009</td>
<td>48 (16-74)</td>
<td>Cyclosporine x 6 mos Dose Cohort 1</td>
<td>10 mg SC on day 1, 20 mg SC on day 2 and 30 mg SC on day 3</td>
<td>ORR 6/17 (35%) Dose 1 6/12 (50%) Dose 2 0/5 = 0% 82% (24 mos)</td>
<td></td>
</tr>
</tbody>
</table>

† - Of note is that 3 patients with sAA were prior Tx with ATG+CsA and 1 previously received Danazol

How can we improve these results?

4 Goals in sAA Treatment

- Relapse Rate
- Clonal Evolution
- Overall Survival

1. OR note is that 3 patients with sAA were prior Tx with ATG+CsA and 1 previously received Danazol
Cyclophosphamide

- Commonly used alkylating agent for chemotherapy and immunosuppression.
- used for AA in 10 patients in Johns Hopkins 45 mg/kg/ D x 4 days (3 of these received concomitant CsA)
- High mortality and morbidity rate particularly with invasive fungal infection was seen in a randomized trial performed by the NIH leading to premature closure of the study
- The most frequently used conditioning regimen before BMT for AA.

Cyclophosphamide (Cytoxan) – Frontline setting

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Median Age (y)</th>
<th>Additional Treatment</th>
<th>Dose</th>
<th>Response Rate</th>
<th>Survival % (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brodsky R. et al. Blood. 2010</td>
<td>44</td>
<td>ATG/ALG, Alemtuzumab, Visilizumab, Cyclophosphamide</td>
<td>Cy 50 mg/kg/D x 4 days + Mesna</td>
<td>Actuarial RR in newly dx pts 19/44 71%</td>
<td>Actuarial Survival rate os 88% at 10 yrs</td>
</tr>
<tr>
<td>Brodsky R. et al. Ann of Int Med. 2001</td>
<td>20</td>
<td>No CsA</td>
<td>Cy 50 mg/kg/D x 4 days + Mesna</td>
<td>Prob of achieving CR at 50 mos is 65%</td>
<td>Survival prob at 24 mos is 84%</td>
</tr>
<tr>
<td>Tisdale JF et al. Lancet. 2000</td>
<td>31†</td>
<td>HD Cy + CsA vs hATG + CsA</td>
<td>HD Cy 35 (18-67) CsA 12 mg/kg/D and adjusted to levels of 200-400 μg/L x 6 mos</td>
<td>46% HD Cy vs 75% ATG at 6 mos excess early mortality (3 deaths within first 3 mos in HD Cy vs 0 in ATG, p=0.101)</td>
<td></td>
</tr>
</tbody>
</table>

**Mechanism of Action**

- **Stem cells**
- **Virus**
- **Naïve T cells**
- **Activated T cells**
- **T cell Activation**
- **T cell Differentiation**
- **T cell Expansion**
- **Effector Mechanisms**
- **Expanded Effector T cells**
- **Effector T cells**
- **APC**
- **Cell-Cell Contact**
- **Cytokine Release**
- **IL-1, IL-6, IL-2, IL-4, IL-6**
- **Cellular Damage**

**Treatment Options**

- **Deposing Agents**
  - ATG/ALG
  - Alemtuzumab
  - Visilizumab
  - Cyclophosphamide

**4 Goals in sAA Treatment At 10 year follow-up**

- **Response Rate**
- **Relapse Rate**
- **Clonal Evolution**
- **Overall Survival**

**How can we improve these results?**

- **Increased response rates**
- **Reduced relapse rates**
- **Improved overall survival**

**Non-Transplant Pharmacologic Treatments (sAA)**

- Cyclophosphamide
- Busulfan
- Fludarabine
- Melphalan
- Melflufen
- Pentostatin
- Thiotepa
- Thiopeta
- Vincristine

**Study**

- Brodsky R. et al. Blood. 2010

**N=67 Retrospective (10 yr ff-up)**

- All patients received G-CSF (5 μg/kg/D) at D 10 until ANC is 1,000 for 2 consecutive days
- Cy 50 mg/kg/D x 4 days + Mesna

**Treatment**

- **G-CSF**
- **Mesna**

**N=19 Phase II**

- All patients received G-CSF (5 μg/kg/D)
- No CsA
- Cy 50 mg/kg/D x 4 days + Mesna

**N=31 Phase III**

- Planned sample size was 91
- **HD Cy + CsA vs hATG + CsA**
  - HD Cy 35 (18-67)
  - CsA 12 mg/kg/D and adjusted to levels of 200-400 μg/L x 6 mos
  - Antimicrobial prophylaxis: Norfloxacin, Pentamidine, fluconazole, acyclovir

- **Response Rate**
- **Survival Rate**
## Non-Transplant Pharmacologic Treatments (sAA)

### Relapsed/ Refractory Setting

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of AA</th>
<th>Median Age (y)</th>
<th>Additional Treatment</th>
<th>Dose</th>
<th>Response Rate</th>
<th>Survival % (mos)</th>
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<tbody>
<tr>
<td>Scheinberg et al. BJH. 2006. N=43</td>
<td>Relapsed/refractory</td>
<td>32 (8-75)</td>
<td>Serum sickness Tx with Prednisone CsA (started D1) 10 mg/kg/D in two divided doses</td>
<td>3,5 mg/kg/D x 5 D</td>
<td>ORR= 65%relapsed 30%refractory</td>
<td>1000 d survival 90% to responders vs 65% in NR</td>
</tr>
<tr>
<td>Di Bona E. et al. BJH. 1999 N=30</td>
<td>Refractory</td>
<td>21 (2-67)</td>
<td>CsA 5 mg/kg PO D1-180 G-CSF 5 μg/kg SC D1-90</td>
<td>3,5 mg/kg/D x 5 D</td>
<td>ORR 23/30 (67%) 9/30 (30%)</td>
<td>93% (~30 mos)</td>
</tr>
</tbody>
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### Rabbit Anti-Thymocyte Globulin (rATG) – Relapsed/ Refractory setting

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### Cyclophosphamide (Cytoxan) Alone – Salvage setting

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Median Age (y)</th>
<th>Additional Treatment</th>
<th>Dose</th>
<th>Response Rate</th>
<th>Survival % (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brodsky R. et al. Exp Hematology. 2004 N=17</td>
<td>-</td>
<td>31 (6-58)</td>
<td>All patients received G-CSF (5 μg/kg/D) at D 10 until ANC is 1,000 for 2 consecutive days</td>
<td>Cy 50 mg/kg/D x 4 days + Mesna</td>
<td>53% achieved a drug free remission. 24% achieved a CR</td>
<td>Actuarial survival rate at 5yrs 52% vs 20% p&lt; 0.05</td>
</tr>
</tbody>
</table>

### Eltrombopag

- Thrombopoietin agonist that stimulates platelet production
- FDA approved for the treatment of Chronic ITP and hepatitis C associated thrombocytopenia

Mechanism of Action of TPO agonists (AMG-531 and Eltrombopag)

<table>
<thead>
<tr>
<th>Mechanism of Action of TPO agonists (AMG-531 and Eltrombopag)</th>
<th></th>
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</thead>
</table>

<table>
<thead>
<tr>
<th>Thrombopoietin Agonist (Mechanism of Action)</th>
</tr>
</thead>
</table>

Relapsed/Refractory AA

Treatment Scheme

Starting dose of 50 mg daily with provision to ↑ dose by 25 mg every 2 weeks if PLT count did not ↑ by 20 x 10^3/μl to a max dose of 150 mg daily.

Response Assessment
Hematologic response defined as uni or trilineage responses (Primary Endpoint)

Non-Transplant Pharmacologic Treatments (sAA)

Eltrombopag (Platelet Response)

Eltrombopag (Hemoglobin Response)

Eltrombopag (Neutrophil Response)
### Non-Transplant Pharmacologic Treatments (sAA)

#### Eltrombopag (Side Effect Profile)

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>N= (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>URTI</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Fever with (+) cultures</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Fever w/o positive culture</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Orthostatic Hypotension</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Shingles</td>
<td>1 (4)</td>
</tr>
<tr>
<td>C diff colitis</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

### Follow-up study using Eltrombopag in Refractory/ Relapsed AA

- Overall Response Rate = 40% (17/43 patients) at 3 to 4 months
- 82% (14/17) pts who went into an extension study continued to show improvement with 7 eventually showing significant ↑ in RBC, ANC and PLT
- 5 patients with robust near normalization of blood counts had drug discontinued at a median of 28.5 months after entry (9 to 37 months) and all maintained stable counts at median of 13 months (range 1-15 months) off eltrombopag
- 8 patients including 6 NR and 2 R developed new cytogenetic abnormalities on Eltrombopag including 5 with chromosome 7 loss or partial deletion but none evolved to AML as of time of publication.

### Special Considerations

- Cyclosporine Taper
- Addition of Growth factors
- Moderate Aplastic Anemia
Supportive

Cyclosporine Taper (slowly taper CsA)

Cumulative incidence of relapse by CsA Discontinuation

Cumulative probability of CsA Discontinuation


Supportive

Growth Factors

- Japanese study of 101 patients with aAA
- Randomized study, median follow-up time of 52 months
- hATG + CsA vs hATG + CsA + G-CSF
- Results:
  - Response Rate at 6 months is better in the G-CSF + arm (77 vs 57 %) p=.03
  - No diff in infection or febrile episodes
  - No diff in survival
  - No diff in MDS/AML evolution (3 % vs G-CSF + arm p=.03)
  - Decreased risk of relapse in G-CSF + arm

Moderate Aplastic Anemia

Daclizumab

- Humanized monoclonal antibody
- Recognizes 55-kDa α-chain of heterodimeric IL-2 receptor
- Has been used in acute rejection in kidney transplantation
- Good toxicity profile.
- Adverse events reported include:
- Severe generalized erythema that can sometimes be associated with arthralgia (usually seen D20-70 after last dose of medication)
- In two patients with thymoma a/t: Hemorrhagic vesicular rash in one a rheumatoid arthritis and reactive airway disease in a second patient

Generalized erythematous pruritic rash

Daclizumab (Zenapax)

As of January 2009, its marketing authorization has been withdrawn and the product discontinued completely

Basiliximab: an anti-IL-2R mAb has been successfully used and reported in 1 case of AA who achieved only a PR after TX with ATG plus MMA and achieved a CR after treatment with basiliximab.

Moderate Aplastic Anemia

Study | Median F/U | Median Age (y) | Additional Treatment | Dose | Response Rate | Survival % (mos)

| Study | Median F/U | Median Age (y) | Additional Treatment | Dose |

Unfortunately

As of January 2009, its marketing authorization has been withdrawn and the product discontinued completely

Basiliximab: an anti-IL-2R mAb has been successfully used and reported in 1 case of AA who achieved only a PR after TX with ATG plus MMA and achieved a CR after treatment with basiliximab.

Conclusions

- ATG remain the standard approach for the management of severe AA although newer agents like Alemtuzumab are showing great promise.
- Horse ATG in combination with cyclosporine is superior to rabbit ATG in combination with CsA in the management of newly diagnosed severe AA.
- Re-treatment with ATG can successfully salvage patients with Aplastic Anemia who previously failed a prior course of ATG.
- Cyclophosphamide show promise as a therapeutic agent but has not gained popularity because of the bad reputation (high mortality rate) it received in the past. It is associated with prolonged cytopenia. Improvement in supportive care management of AA including anti-fungals may allow for improvement in its safety profile.
- Eltrombopag is a thrombopoietin agonist that can lead to improvements in hemoglobin, platelet counts and neutrophil counts in AA patients who have previously failed immunosuppressive agents.

Thank You.